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THIAMIN YLIDE: ISOLATION AND IDENTIFICATION

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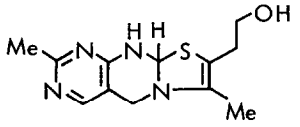
Abstract: The action of two equivalents of NaOEt on thiamin hydrochloride in EtOH gives a neutral compound. Spectroscopic data and its chemical behavior indicated that the compound is thiamin ylide 1. The chemical behaviors of 1 are entirely consistent with those of in situ generated thiamin ylide.

Thiamin ylide 1 plays a central role in both the coenzymatic reaction of vitamin B_1 as well as the nonenzymatic reaction, e.g., acyloin condensation. Its formation was proposed by Breslow[1] based on the H-D exchange reaction of C-2 proton of thiazolium salt. Although the concept of 1 is widely accepted and the structure of 1 is simply a conjugate base of thiamin, there has thus far been no report of its isolation.

Maier and Metzler[2] have reported the isolation of the salt-free alkoxide-neutralized product of thiamin hydrochloride (2a) to which 2,7-dimethyl-9a,10-dihydro-5H-thiachromine-8-ethanol 3 was assigned. They described the UV data and some of its chemical properties which indicated that product 3 is highly reactive. Risinger et al.[3] reexamined Metzler's experiment and concluded on the basis of a temperature dependent NMR study, that the structure of the alkoxide-neutralized product of 2a was 2,6-dimethyl-6a,8,9,9a,10a,11-hexahydro-5H-furo[2,3-h]thiachromine 4, which changed thermally into 3.



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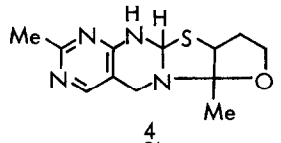

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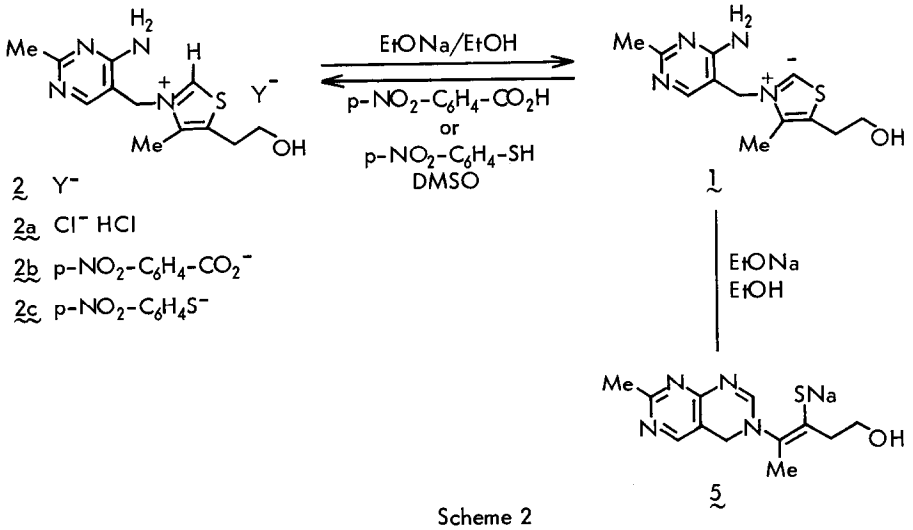
Scheme 1

To obtain further information on the structure of the alkoxide-neutralized form of 2a, we carried out Metzler's experiment. Our conclusion is that the conjugate base of 2a is thiamin ylide 1, based on the following spectroscopic considerations and chemical behaviors toward electrophiles which were the same as those of in-situ generated 1. Compound 1 was isolated according to the following procedure. To a cooled suspension of 10.0 g (29.6 mmol) of thiamin hydrochloride in 25 mL of EtOH was added dropwise at 5 °C two equivalents of NaOEt solution, which had been prepared from 1.38 g (60 mg atom) of Na in 25 mL of EtOH. After the mixture had been stirred for

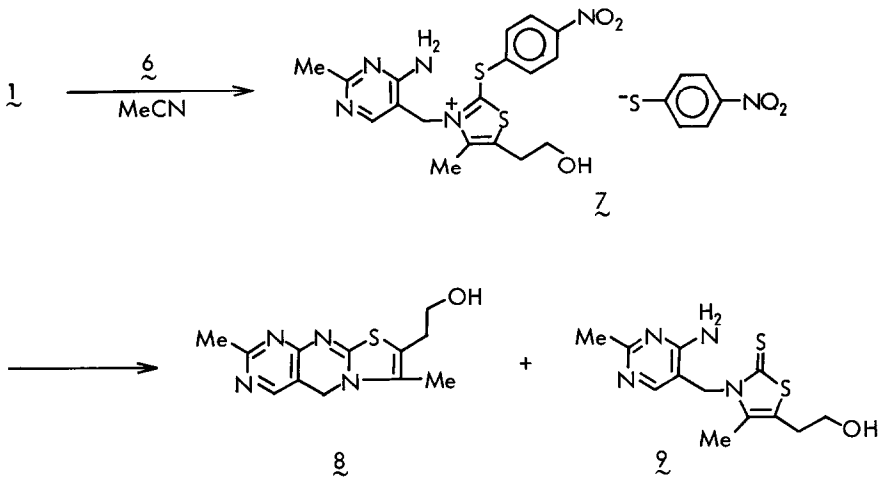
15 min at 5 °C, it was filtered under nitrogen.[4] The filtrate was allowed to stand overnight at -20 °C and then separated by filtration under nitrogen, giving 300 mg (3.8% yield) of slightly hygroscopic colorless product 1 in analytically pure state: mp 127-129 °C; UV λ_{max} (EtOH) nm (log ε), 236 (4.08), 270 (3.81): IR (Nujol) cm^{-1} 3100, 1655, 1610, 1570, 1525, 1290, 1060, 1040; ^1H NMR (DMSO-d_6) δ 1.65 (s, 3 H, thiazole-Me), 2.29 (s, 3 H, pyrimidine-Me), 2.35 (br t, 2 H, $\underline{CH_2}CH_2OH$), 3.40 (m, 2 H, $CH_2\underline{CH_2}OH$), 4.17 (br s, 2 H, bridge CH_2), 4.44 (br t, 1 H, OH), 6.35 (s, 1 H, NH), 7.28 (br s, 1 H, NH), 7.84 (s, 1 H, pyrimidine-H). H-D exchange of the OH and NH signals occurred on addition of CD_3OD; the ^{13}C NMR spectrum in DMSO-d_6 explicitly exhibited ten carbons implying degeneracy and/or negligible intensity for the remaining two carbons, δ 10.6 (thiazole-Me), 25.2 (pyrimidine-Me), 31.4 ($\underline{CH_2}CH_2OH$), 42.2 (bridge CH_2), 60.4 ($CH_2\underline{CH_2}OH$), 104.8 (pyrimidine-C_5), 131.2 (thiazole), 149.5 (pyrimidine-C_6), 158.4 (thiazole), 165.3 (pyrimidine-C_2 and/or C_4); Anal. Calcd for $C_{12}H_{16}N_4OS \cdot 1/5 \cdot H_2O$: C, 53.79; H, 6.17; N, 20.91; S, 11.96. Found: C, 53.90; H, 6.09; N, 20.71; S, 11.78. High resolution mass spectrometry; Calcd for $C_{12}H_{16}N_4OS$ m/e 264.1043. Found m/e = 264.1043; m/e (relative intensity %, chemical formula) 31 (31%, CH_3O), 85 (36%, C_4H_5S), 112 (100%, C_5H_6NS), 122 (34%, $C_6H_8N_3$), 143 (19%, C_6H_9NOS), 148 (13%, $C_7H_8N_4$), 233 (14%, $C_{11}H_{13}N_4S$), 264 (12%, M^+). With iteration of the mass scanning, the fragmentation pattern changed, that is, new peaks at m/e 284 ($C_{12}H_{16}N_2O_2S_2$), 253 (284-CH_3O) and 222 (253-CH_3O) appeared at the expense of the molecular ion peak.

The UV spectrum of 1 is different from that described for the tricyclic compound 3 by Maier and Metzler.[2] NMR data of 3 are not available except for Risinger's report.[3] The C_{9a}-H bond of 3 is structurally related to that of C_{10a}-H in 4. The structure and the chemical behavior of the tetracyclic compound 4 has well been established by X-ray analysis[5] and variable temperature NMR study in which 4 proved to be highly stable chemically as well as thermally.[6] Thus, the stability of 4 contradicts Risinger's assumption. ^1H NMR data of a mixture of conformational isomers of 4 revealed that the chemical shift of C_{10a}-H in DMSO-d_6 was observed at δ 5.86 and 6.03 and ^{13}C NMR of 4 showed resonance for the C_{10a} carbon at δ 78.5. Ylide 1 has no such absorption, which rules out the possibility of the structure of the neutralized product of 2 being either 3 or 4.

Treatment of 1 with excess EtONa in EtOH afforded a yellow solution, which gave a UV spectrum with absorption at 253 and 334 nm indicating the formation of 5.[7] On the other hand, the 1:1 adduct of 1 with p-nitrobenzoic acid or p-nitrothiophenol has been found to be the thiazolium salt 2b or 2c, respectively, based on NMR spectroscopy.[8] These findings clearly demonstrated the protonation of 1 and the role of 1 as an intermediate in the equilibrium between 2 and 5. The carbanion like character of 1 was further confirmed by the electrophilic reaction of di-p-nitrophenyldisufide 6 toward 1.[9] Treatment of 1 with an equivalent of disulfide 6 in MeCN for 3 h at room temperature



Scheme 2



Scheme 3

gave a dark red unstable solid 7, of which structural proof rested on its NMR and UV data. Thiazolium salt 7 underwent intramolecular nucleophilic attack on refluxing in MeCN for 3 h with disappearance of the red color giving about a 1:1 mixture of thiochrome 8 and 2(3H)-thiazolethione derivative 9.[10] Finally, catalytic acyloin condensation reaction of 1 was carried out under neutral condition. Ylide 1 was allowed to react with six equivalents of 2-furaldehyde 10 in EtOH at 0 °C to room temperature for 2 h. Work up with column chromatography on silica gel yielded furoin in 81% yield based on 10, which indicated that the active aldehyde was produced under very mild and neutral conditions using 1. Usually in situ generation of 1 requires

heating of a mixture of 2 and an appropriate base such as NEt_3 in the presence of an electrophile.[11]

These chemical behaviors are completely consistent with those of in situ generated 1. Further studies on the reactivity of the isolated 1 are now in progress.

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(10) The formation of 9 and 8 can best be explained by either (a) ipso substitution of the SAr moiety by a counter anion or (b) intramolecular nucleophilic attack of the amino group to C-2 of the thiazolium ring to give C_9-SAr substituted-dihydrothiochrome. Elimination of ArSH leads to the formation of 8.

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